

**Thiazole, Imidazole and Oxazole Compounds and Treatments of Disorders  
Associated with Protein Aging**

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5 Sub A1 This application claims the priority of the following applications: Application No. 60/176,995, filed 19-January-2000; No. 60/183,274, filed 17-February-2000; No. 60/259,291, filed 29-December-2000 (~~Attny. Docket 361331-501 P7D~~); No. 60/259,237, filed 2-January-2001 (~~Attny. Docket 361331-501 P7E~~); No. 60/259,107, filed 29-December-2000 (~~Attny. Docket 361331-501 P7F~~), and No. 60/259,237, filed 2-January-2001 (~~Attny. Docket 361331-501 P7A~~).

The present invention relates to methods for treating certain fibrotic diseases or other indications.

Glucose and other sugars react with proteins by a non-enzymatic, post-translational modification process called non-enzymatic glycosylation. At least a portion of the resulting sugar-derived adducts, called advanced glycosylation end products (AGEs), mature to a molecular species that is very reactive, and can readily bind to amino groups on adjacent proteins, resulting in the formation of AGE cross-links between proteins. Recently a number of classes of compounds have been identified whose members inhibit the formation of the cross-links, or in some cases break the cross-links. These compounds include, for example, the thiazolium compounds described in US Patent No. 5,853,703. As AGEs, and particularly the resulting cross-links, are linked to several degradations in body function linked with diabetes or age, these compounds have been used, with success, in animal models for such indications. These indications include loss of elasticity in blood vasculature, loss of kidney function and retinopathy. Now, as part of studies on these compounds, it has been identified that these compounds inhibit the formation of bioactive agents, such as growth factors and inflammatory mediators, that are associated with a number of indications. These agents include vascular endothelial growth factor (VEGF) and TGF[beta]. As a result, a number of new indications have been identified for treatment with agents that inhibit the formation of, or more preferably break, AGE-mediated cross-links. It is not unreasonable to infer that the effects seen are due to the removal of AGE-related molecules that provide a stimulus for the production or release of these growth factors. Removal of such molecules is believed to proceed in part due to the elimination of AGE-related cross-links that lock the AGE-modified proteins in place. Moreover, such compounds also reduce the expression of

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